Epidemiological and Molecular Studies of Holoprosencephaly in South America (ECLAMC)

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ECLAMC: Latin American Study of Congenital Malformations has examined in South American hospitals 4,157,224 births since 1967, detecting 370 newborns with a face suggestive of holoprosencephaly (HPE): 182 (49.2%) had only craniofacial defects, 99 (26.8%) had also defects in other systems, 56 (15.1%) had chromosomal anomalies, 26 (7.6%) had premaxillary agenesis (without neuroimaging results), and 5 (1.4%) had known syndromes. The syndromes diagnosed in the first week of life were Pseudo-trisomy 13, Thanatophoric dysplasia, Aicardi, Genoa, and Meckel-Gruber syndromes. There were 41 cases of trisomy 13, 4 cases of trisomy 18, one case of triploidy, and two other anomalies among the chromosomal anomalies group. The isolated, associated, and chromosomal anomalies groups had the same proportion of cyclopia; the chromosomal anomalies group had less hydrocephaly and more premaxillary agenesis than the other 2 groups. The 74% of perinatal mortality precluded karyotyping of most of the cases.

The birth prevalence of the isolated HPE was homogeneous among the eleven Latin American sampled countries, and it has increased from 0.5 to 1 per 10,000 births in the last 4 years, probably due to better ascertainment trough ultrasound. The group with premaxillary agenesis lacking neuroimaging differed from isolated, associated and chromosomal anomalies groups, presenting an excess of male sex and better survival with only 11% of perinatal deaths. The HPE group with chromosomal anomalies had higher maternal age than the other 3 groups. The groups with chromosomal and associated anomalies had higher frequency of low birth weight, perinatal mortality, and intersex than the isolated group. The isolated, associated and chromosomal anomalies groups did not differ about the normal gestational age, excess of female sex and higher frequency of twins.

We did not confirm the described association of isolated HPE with maternal anemia or with aspirin use in the first trimester of gestation; the described association of HPE and maternal respiratory illness was confirmed for the flu subgroup; the known association of HPE and maternal diabetes and/or insuline use, was only demonstrated for the isolated and associated groups considered together; sexual hormones were found associated with isolated HPE, and also vaginal bleeding in the first trimester of pregnancy. We had few or no cases of isotretinoin, anticonvulsants and/or maternal epilepsy, which are other associated factors described in the literature.

Since 1999 ECLAMC are collecting blood spots from newborn with HPE to search for molecular defects. In the period 1999-2000, 30 patients were studied for four genes, *Sonic hedgehog* (*SHH*), *ZIC2*, *SIX3*, and the TG-interacting factor (*TGIF*) gene. Two heterozygous mutations in *SHH*, G699T and A570C, and a 2-bp deletion (860-861) in the zinc-finger domain of *ZIC2* gene were described. Further 32 HPE patients from the 2001-2002 period have being studied for *SHH* exon 2. A new heterozygous mutation, T633A, resulting in a Leu161Gln substitution was found.

References:

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